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EXAMINER	
TON, THAIAN N	

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1632	

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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/595,619	VON DER KAMMER ET AL.	
	Examiner	Art Unit	
	Thaian N. Ton	1632	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *19 December 2008*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-28* is/are pending in the application.

4a) Of the above claim(s) *1-3,5-11,13-18 and 24-28* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *4-8,12 and 19-23* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *01 May 2006* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Claims 1-28 are pending; claims 1-3, 5-11, 13-18, 24-28 are withdrawn; claims 4-8, 12 and 19-23 are under current examination.

Election/Restrictions

Applicant's election without traverse of Group III (claims 4-8, 12, 19-23) in the reply filed on 12/19/08 is acknowledged.

Claims 1-3, 5-11, 13-18 and 24-28 withdrawn from further consideration pursuant to 37 CFR 1.142(b) as being drawn to a nonelected groups, there being no allowable generic or linking claim. Election was made without traverse in the reply filed on 12/19/08.

Claim Objections

Claim 12 is dependent on a non-elected claim. Specifically, claim 12 depends from claim 11. Applicants have elected methods of utilizing a genetically altered non-human animal. Therefore, it is suggested that claim 12 be written to incorporate the limitations of claim 12.

Claim Rejections - 35 USC § 101/112

35 U.S.C. 101 reads as follows:

> Whoever invents or discovers any new and useful process, machine, manufacture, or composition of matter, or any new and useful improvement thereof, may obtain a patent therefor, subject to the conditions and requirements of this title.

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Definitions:

[from REVISED INTERIM UTILITY GUIDELINES TRAINING MATERIALS; repeated from http://www.uspto.gov/web/menu/utility.pdf]

"Credible Utility" - Where an applicant has specifically asserted that an invention has a particular utility, that assertion cannot simply be dismissed by Office personnel as being "wrong". Rather, Office personnel must determine if the assertion of utility is credible (i.e., whether the assertion of utility is believable to a person of ordinary skill in the art based on the totality of evidence and reasoning provided). An assertion is credible unless (A) the logic underlying the assertion is seriously flawed, or (B) the facts upon which the assertion is based is inconsistent with the logic underlying the assertion. Credibility as used in this context refers to the reliability of the statement based on the logic and facts that are offered by the applicant to support the assertion of utility. A *credible* utility is assessed from the standpoint of whether a person of ordinary skill in the art would accept that the recited or disclosed invention is currently available for such use. For example, no perpetual motion machines would be considered to be currently available. However, nucleic acids could be used as probes, chromosome markers, or forensic or diagnostic markers. Therefore, the credibility of such an assertion would not be questioned, although such a use might fail the *specific* and *substantial* tests (see below).

"Specific Utility" - A utility that is *specific* to the subject matter claimed. This contrasts with a *general* utility that would be applicable to the broad class of the invention. For example, a claim to a polynucleotide whose use is disclosed simply as a "gene probe" or "chromosome marker" would not be considered to be *specific* in the absence of a disclosure of a specific DNA target. Similarly, a general statement of diagnostic utility, such as diagnosing an unspecified disease, would ordinarily be insufficient absent a disclosure of what condition can be diagnosed.

"Substantial utility" - a utility that defines a "real world" use. Utilities that require or constitute carrying out further research to identify or reasonably confirm a "real world" context of use are not substantial utilities. For example, both a therapeutic method of treating a known or newly discovered disease and an assay method for identifying compounds that themselves have a "substantial utility" define a "real world" context of use. An assay that measures the presence of a material which has a stated correlation to a predisposition to the onset of a particular disease condition would also define a "real world" context of use in identifying potential candidates for preventive measures or further monitoring. On the other hand, the following are examples of situations that require or constitute

carrying out further research to identify or reasonably confirm a "real world" context of use and, therefore, do not define "substantial utilities":

A. Basic research such as studying the properties of the claimed product itself or the mechanisms in which the material is involved.

B. A method of treating an unspecified disease or condition. (Note, this is in contrast to the general rule that treatments of specific diseases or conditions meet the criteria of 35 U.S.C. 101.)

C. A Method of assaying for or identifying a material that itself has no "specific and/or substantial utility".

D. A method of making a material that itself has no specific, substantial, and credible utility.

E. A claim to an intermediate product for use in making a final product that has no specific, substantial, and credible utility.

Note that "throw away" utilities do not meet the tests for a *specific* or *substantial* utility. For example, using transgenic mice as snake food is a utility that is neither specific (all mice could function as snake food) nor substantial (using a mouse costing tens of thousands of dollars to produce as snake food is not a "real world" context of use). Similarly, use of any protein as an animal food supplement or a shampoo ingredient are "throw away" utilities that would not pass muster as specific or substantial utilities under 35 U.S.C. ' 101. This analysis should, or course, be tempered by consideration of the context and nature of the invention. For example, it a transgenic mouse was generated with the specific provision of an enhanced nutrient profile, and disclosed for use as an animal food, then the test for specific and substantial *asserted* utility would be considered to be met.

"Well established utility" - a specific, substantial, and credible utility which is well known, immediately apparent, or implied by the specification's disclosure of the properties of a material, alone or taken with the knowledge of one skilled in the art. "Well established utility" does not encompass any "throw away" utility that one can dream up for an invention or a nonspecific utility that would apply to virtually every member of a general class of materials, such as proteins or DNA. If this is the case, any product or apparatus, including perpetual motion machines, would have a "well established utility" as landfill, an amusement device, a toy, or a paper weight; any carbon containing molecule would have a "well established utility" as a fuel since it can be burned; any protein would have well established utility as a protein supplement for animal food. This is not the intention of the statute.

See also the MPEP § 2107 - 2107.02.

Claims 4-8, 12 and 19-23 are rejected under 35 U.S.C. 101 because the claimed invention is not supported by either a specific and substantial asserted utility or a well established utility.

The claimed invention is directed to a genetically altered non-human animal comprising a non-native gene sequence coding for DAX-1, or a fragment, derivative or variant thereof. Further embodiments limit the species of animal to mammal or invertebrate. Additional embodiments limit the phenotype of the animal. Further embodiments are directed to utilizing the animal to develop diagnostics and therapeutics to treat neurodegenerative diseases.

The specification teaches the generation of human DAX-1 transgenic flies. In particular, the specification teaches that a DAX-1 vector was inserted downstream of the UAS-binding sites and P-element mediated germline transformation was performed and 26 independent DAX-1 transgenic fly lines were generated. To characterize the potential impact of human DAX-1 expression on neuropathology associated with amyloidogenic processing of human Application, DAX-1 was co-expressed with $hAPP_{695}$ and human BACE in the adult retina (p. 46, last full ¶). The specification teaches that over-expression of DAX-1 in the adult retina has no impact on proper assembly and differentiation of photoreceptor cells. Expression of hAPP and hBACE leads to age-dependent degeneration of photoreceptor cells, whereas co-expression of DAX-1 leads to rescue of the degenerative phenotype in young and aging flies (p. 47, 2nd ¶). Additionally, amyloid plaque deposition in the retina of hAPP/hBACE expressing flies is accelerated by co-expression of mutant forms of presenilin, and that co-expression with DAX-1 shows a delayed onset of plaque deposition (p. 47, last full ¶). The specification teaches that to characterize the neuroprotective effect of DAX-1 on photoreceptor cell degeneration, eye specific expression of bTAU induces a severe, age-degeneration of photoreceptors in the

adult retina, and co-expression of DAX-1 rescues the photoreceptor cell degeneration.

The specification teaches the production of DAX-1 transgenic mice, wherein the mice expressed human DAX-1 cDNA in neuronal cells (p. 47 #ix). The spec teaches that the targeting vector was transfected into mouse ES cells, and after homologous recombination, the ES cell clones were identified and injected into blastocysts to produce chimeric mice. After successful germline transmission of chimeric mice, the mice were then crossed to an Alzheimer's disease mouse model to produce transgenic DAX-1 mice on an Alzheimer's disease background. The specification provides no specific phenotype of the resultant mice.

The instant specification teaches that DAX-1 is found in human AD brain samples (p. 2, last ¶). The specification further teaches that the function of DAX-1 is as a transcriptional repressor (p. 4) and that the expression of DAX-1 is speculated to be regulated by the steroidogenic factor 1 (p. 5). The specification teaches that DAX-1 mRNA levels are higher in temporal cortex and hippocampus areas as compared to the frontal cortex in AD patients, and that DAX-1 mRNA levels are elevated in the temporal cortex, but not the frontal cortex of AD-patients. The specification speculates that the dysregulation of DAX-1 expression may lead to a pathological alteration of cholesterol homeostasis in AD-affected brains, and could potentially lead to irreversible neuronal damage. The specification teaches that to date, no experiments have been described that demonstrate a relationship between the dyregulation of DAX-1 gene expression and the pathology of neurodegenerative disease, such as AD. See p. 5, last sentence and pages 12-13, bridging sentence.

Thus, the specification teaches dysregulation of DAX-1 expression, and suggests a putative link between the up-regulation of DAX-1 and diagnosis and treatment of neurodegenerativediseases, such as AD (see p. 13, 1st ¶, last sentence). However, at the time of filing, the skilled artisan would not have found any of the contemplated utilities as evidence of utility because neither the art, nor the

specification, provide a correlation between the up-regulation/over-expression of DAX-1 and neurodegenerative diseases, such as AD. The specification provides, at best, a prophetic suggestion of DAX-1's role in AD, but there is no clear teaching in the specification with regard the actual function of DAX-1 in AD, other than the overexpression data. One of skill in the art could not rely upon the state of the art because as stated by the specification, there have been no experiments that demonstrated any relationship between dysregulation of DAX-1 gene expression and the pathology of neurodegenerative diseases, such as AD. The teachings of the art, at the time of filing, and the specification, provide no guidance with regard to the function of the protein encoded by DAX-1 with respect to any neurodegenerative disease. Thus, any correlation between the mutation of this particular gene and a particular disease cannot be determined.

If the function of a gene, or its encoded protein, is not known in the art, or disclosed in the specification at the time of filing, the utility of the claimed invention is not apparent. It is further noted that the specification only teaches rescue of flies in DAX-1 coexpression assays. The specification provides no guidance for transgenic animals only expressing DAX-1. Therefore, the results in the specification fail to provide guidance with respect to the role of DAX-1 in any neurodegenerative disease. Certain claimed embodiments recite that the expression of DAX-1 results in a predisposition to development of symptoms of neuropathology similar to a neurodegenerative disease (see claim 6, for example). The results in the specification fail to provide any guidance to show that DAX-1's expression results in symptoms of neuropathology of any neurodegenerative disease because the working examples are directed to rescuing a degenerative phenotype when co-expressing DAX-1. Thus, specification provides no evidence that these phenotype of the rescued flies would be accepted as evidence of a particular biochemical pathway, a particular disease/condition, or as evidence of either a substantial or specific utility. As set forth in the utility guidelines summarized

above, a general statement of diagnostic utility, such as diagnosing an unspecified disease, would ordinarily be insufficient, absent a disclosure of what condition can be diagnosed. Similarly, a statement of therapeutic utility for an unspecified disease is non-specific, renders the purported utility of the claimed mice to be non-specific. The usefulness of the mutant mice, as models for disease, is not clear absent the assessment that they reflect a particular disease state. This leaves the skilled artisan to speculate the uses of the mice, cells, and methods, as claimed. Under the utility guidelines set forth above, requirement for further research or experimentation renders the claimed invention as lacking in a specific or substantial utility. Utilities that require or constitute carrying out further research to identify or reasonably confirm a "real-world" context of use are not considered substantial utilities. The evidence of record has not provided any other utilities for the transgenic non-human animals encompassed by the claims that are substantial and specific.

Furthermore, the use of the transgenic animals in determining function of the DAX-1 gene is not sufficient for utility because the relationship between the observed phenotypes and gene function do not necessarily correlate. Additional research would be required based on the present disclosure to determine if the phenotypes were related to DAX-1 gene function.

Enablement

Claims 4-8, 12 and 19-23 are also rejected under 35 U.S.C. 112, first paragraph. Specifically, since the claimed invention is not supported by either a specific and substantial asserted utility or a well established utility asserted utility or a well established utility for the reasons set forth above, one skilled in the art clearly would not know how to use the claimed invention.

Claims 4-8, 12 and 19-23rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement. The claim(s) contains subject

matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

Enablement is considered in view of the Wands factors (MPEP 2164.01(A)). These include: nature of the invention, breadth of the claims, guidance of the specification, the existence of working examples, state of the art, predictability of the art and the amount of experimentation necessary. All of the Wands factors have been considered with regard to the instant claims, with the most relevant factors discussed below.

Nature of the Invention. The claimed invention is directed to a genetically altered non-human animal comprising a non-native gene sequence coding for DAX-1, or a fragment, derivative or variant thereof. Further embodiments limit the species of animal to mammal or invertebrate. Additional embodiments limit the phenotype of the animal. Further embodiments are directed to utilizing the animal to develop diagnostics and therapeutics to treat neurodegenerative diseases.

Breadth of the claims. The breadth of the claims encompass any species of animal, wherein the animal has symptoms resulting any disease, and specifically any neurodegenerative disease. Additionally, the breadth of the claims encompasses any fragment, derivative or variant of DAX-1 used to produce a transgenic animal,

Guidance of the Specification/The Existence of Working Examples. The specification teaches the generation of human DAX-1 transgenic flies. In particular, the specification teaches that a DAX-1 vector was inserted downstream of the UAS-binding sites and P-element mediated germline transformation was performed and 26 independent DAX-1 transgenic fly lines were generated. To characterize the potential impact of human DAX-1 expression on neuropathology associated with amyloidogenic processing of human Application, DAX-1 was co-expressed with $hAPP_{695}$ and human BACE in the adult retina (p. 46, last full ¶). The specification

teaches that over-expression of DAX-1 in the adult retina has no impact on proper assembly and differentiation of photoreceptor cells. Expression of hAPP and hBACE leads to age-dependent degeneration of photoreceptor cells, whereas co-expression of DAX-1 leads to rescue of the degenerative phenotype in young and aging flies (p. 47, 2nd ¶). Additionally, amyloid plaque deposition in the retina of hAPP/hBACE expressing flies is accelerated by co-expression of mutant forms of presenilin, and that co-expression with DAX-1 shows a delayed onset of plaque deposition (p. 47, last full ¶). The specification teaches that to characterize the neuroprotective effect of DAX-1 on photoreceptor cell degeneration, eye specific expression of bTAU induces a severe, age-degeneration of photoreceptors in the adult retina, and co-expression of DAX-1 rescues the photoreceptor cell degeneration.

The specification teaches the production of DAX-1 transgenic mice, wherein the mice expressed human DAX-1 cDNA in neuronal cells (p. 47 #ix). The spec teaches that the targeting vector was transfected into mouse ES cells, and after homologous recombination, the ES cell clones were identified and injected into blastocysts to produce chimeric mice. After successful germline transmission of chimeric mice, the mice were then crossed to an Alzheimer's disease mouse model to produce transgenic DAX-1 mice on an Alzheimer's disease background. The specification provides no specific phenotype of the resultant mice.

State of the Art/Predictability of the Art. MPEP §2164.03 states that, "The amount of guidance or direction needed to enable the invention is inversely related to the amount of knowledge in the state of the art as well as the predictability in the art. ... The "predictability or lack thereof" in the art refers to the ability of one skilled in the art to extrapolate the disclosed or known results to the claimed invention. If one skilled in the art can readily anticipate the effect of a change within the subject matter to which the claimed invention pertains, then there is predictability in the art. On the other hand, if one skilled in the art cannot readily

anticipate the effect of the change within the subject matter to which the claimed invention pertains, there is a lack of predictability in the art. Accordingly, what is known in the art provides evidence as to the question of predictability."

The invention is broadly directed to the genus of any genetically altered non-human animal comprising a non-native gene sequence coding for DAX-1, a fragment or a derivative or variant thereof. The instant specification teaches that DAX-1 is found in human AD brain samples (p. 2, last ¶). The specification further teaches that the function of DAX-1 is as a transcriptional repressor (p. 4) and that the expression of DAX-1 is speculated to be regulated by the steroidogenic factor 1 (p. 5). The specification teaches that DAX-1 mRNA levels are higher in temporal cortex and hippocampus areas as compared to the frontal cortex in AD patients, and that DAX-1 mRNA levels are elevated in the temporal cortex, but not the frontal cortex of AD-patients. The specification speculates that the dysregulation of DAX-1 expression may lead to a pathological alteration of cholesterol homeostasis in AD-affected brains, and could potentially lead to irreversible neuronal damage. The spec teaches that to date, no experiments have been described that demonstrate a relationship between the dyregulation of DAX-1 gene expression and the pathology of neurodegenerative disease, such as AD. See p. 5, last sentence. The specification provides no guidance for a genetically altered comprising a non-native gene sequence coding for DAX-1, other than the co-expression of DAX-1 with various other genes (see examples, pages 46-47). However, these rescue assays fail to provide a specific role or elucidation of function for DAX-1 in any neurodegenerative disease. In particular, the working examples fail to provide guidance to show that an animal that expresses DAX-1 would have a phenotype of 1) a predisposition to developing symptoms of a neuropathology similar to a neurodegenerative disease (claim 6); or 2) a reduced risk of developing symptoms similar to a neurodegenerative disease. There is no guidance that simply expressing DAX-1 would result in the phenotypes that are encompassed by the claims. Additionally,

the specification only describes experiments in Drosophila. Although the specification discusses the production of DAX-1 transgenic mice, there is no discussion of the phenotype of these mice. The specification does not provide enablement for the breadth of species of animals encompassed by the genus of non-human transgenic animals, which include, for example, nematodes, avian, reptiles, and insects. The generation of a particular transgenic animal requires a specific vector that expresses a specific candidate gene, which produces a specific effect. The specification provides no specific effect of the DAX-1 transgene expression, with respect toe a specific phenotype in the resultant animal. One of skill in the art, given the limited teachings provided by the specification, could not rely upon the state of the art of producing transgenic animals, to predictably produce a transgenic non-mammalian animal with a specific phenotype.

This is because the state of the art is unpredictable with regard to generating transgenic animals with a predictable phenotype. The breadth of the claims encompass any non-mammalian transgenic animals (claim 4), and any mammal or invertebrate (claim 5). This encompasses a wide variety of animals that are extremely diverse. For example, Encarta Online Encyclopedia (2008) states that, "Invertebrates are by far the most numerous animals on Earth. Nearly 2 million species have been identified to date. These 2 million species make up 98 percent of all the animals identified in the entire animal kingdom. Some scientists believe that the true number of invertebrate species may be as high as 100 million." See 1st paragraph. Thus, given that invertebrates themselves make up such a large number of species, one of skill in the art could not predict what phenotype would result from the introduction of a non-native gene sequence coding for DAX-1, a fragment or derivative or variant thereof, into the genome of any of the millions of species of animals encompassed by the claims. It is noted that the specification only discusses using the full length DAX-1 sequence, and provides no guidance for any phenotype of any animal produced using a fragment, derivative or variant of DAX-1,

therefore it would be unpredictable as to what phenotype(s) the resultant animal would have.

The art of producing transgenic insects, for the breadth claimed is unpredictable. O'Kane **(Sem. In Cell & Dev. Bio.**, 14: 3-10, 2003) state that although flies and worms have homologues of various human genes, the phenotype of the resultant transgenic animal depends upon the gene that is being introduced. They state, "[A] major limitation is that fewer than half the genes in the genome currently have an insertion in or near them, and not all of these insertions will disruption gene function sufficiently to give an obvious mutant phenotype." Page 4, col. 1, #1, last sentence. They further teach that using flies and worms as disease models can have obscured later phenotypes if the mutation is lethal in early development (p. 4, #2). They further teach that even though flies, worms and humans have some homologous genes, there is no consensus on how related these species are, each to the other, which leads to questioning how pertinent a model fly or worm are for a particular process or disease (p. 5-6, #3.1, Shared History). They further teach the differences between flies, worms and human, for example, that humans have two or more duplicated forms of genes that are usually only present in one copy in flies or worms. They teach that, "In conclusion, flies and worms will be more useful models for some processes than for other. It would be foolish to assume that because something works in a certain way in flies or worms, that it must automatically work like this in humans." See page 6, 2nd column, 2nd full ¶.

Furthermore, Robinson *et al.* **(Insect Biochem. And Mol. Bio.**, 34: 113-120, 2004) support the unpredictability in producing transgenic insects, stating that the P-element based vectors that were successful in transforming Drosophila were unable to be used in other insects because the P-element system required host-specific factors that were species specific (p. 114, col. 1-2, bridging ¶). They teach that although there have been advances in producing vectors (including transposon-based gene vectors) to produce transgenic insects, there is wide distribution and

host range and that limited information is available about the mobile element interaction with the host genome and the ability to move between species. They clearly teach that the art of producing transgenic insects is undeveloped stating that, "Safe and effective implementation of transgenic systems to a broad variety of insect pests will require methods to ensure vector stability and strain integrity, while maintaining consistent levels of transgene expression." See p. 115, 1st col., 1st ¶. Wimmer (**Nature Reviews**, 4: 225-232, March 2003) state that using Drosophila transgenic technology, "Hopes were raised that transgenic approaches would be applied to other insect species ... However, despite great efforts, the P element seems not to be functional outside the Drosophilids' because of host-specific co-factor requirements." See page 225, col. 1-2. Wimmer discusses the factors that are required for successful transgenesis in insects, including the appropriate species-specific promoter(p. 225, 3rd col), and the determination of coding and non-coding regions of a species' genome, as well as the corresponding biological function (p. 228, 3rd col. Functional Insect Genomics).

The undeveloped and unpredictable state of the art of producing transgenic animals, including invertebrate, shows that since there is limited knowledge with regard to how to produce the breadth of animals encompassed by the claims, with a specific phenotype, the art provides little upon which to base a prediction. Therefore, if one has no basis for making a prediction, the outcome is necessarily unpredictable. One of skill in the art could not use the art of producing transgenic mammals, which is far more developed than the non-mammalian art, because there is wide diversity in the resultant phenotype, and that the effect of one transgene cannot be predicted from one species to another. This is because the art of transgenic animals has for many years stated that the unpredictability lies with the site or sites of integration of the transgene into the target genome.

Transgenic animals are regarded to have within their cells cellular mechanisms which prevent expression of the transgene, such as DNA methylation

or deletion from the genome (Kappell et al (1992) Current Opinion in Biotechnology 3, 549, col. 2, parag. 2). Mullins et al (1993), cited on Applicants' IDS, filed 10/4/05, states that not all animals express a transgene sufficiently to provide a model for a disease as the integration of a transgene into difference species of animal has been reported to given divergent phenotypes (Mullins et al (1993) Hypertension 22, page 631, col. 1, parag. 1, lines 14-17). The elements of the particular construct used to make transgenic animals are held to be critical, and that they must be designed case by case without general rules to obtain good expression of a transgene; e.g., specific promoters, presence or absence of introns, etc. Well-regulated transgenic expression is not frequently achieved because of poor levels or the complete absence of expression or leaky expression in non-target tissues (Cameron (1997) Molec. Biol. 7, page 256, col. 1 -2, bridg. parag.). Factors influencing low expression, or the lack their of, are not affected by copy number and such effects are seen in lines of transgenic mice made with the same construct (Cameron (1997), Molec. Biol. 7, page 256, lines 3-9). These factors, thus, are copy number independent and integration site dependent, emphasizing the role the integration site plays on expression of the transgene (Cameron (1997), Molec. Biol. 7, page 256, lines 10-13).

Additionally, Clark *et al.* (**Nature Reviews**: 4: 825-833, 2003) reviews the state of the art of transgenic livestock, state that, "Pro-nuclear injection enables only the random addition of genes to the germline. It does not allow the precise modificdation of the germline that is required for the specific deletion or modification of endogenous genes. A high proportion of transgenic lines that pro-nuclear injection generates do not efficiently express transgenes because of silencing effects at the site of integration." See p. 827, col. 3 Gene Targeting. In particular, they teach discuss that techniques for knocking out, or specific integration of a particular gene was established in the mouse, and that, "Unfortunately, despite intensive efforts, this technology is limited to the mouse, as

no germline-competent ES cells have been described for any other mammalian species." See p. 828, col. 1, 1st full ¶.

While, the intent is not to say that transgenic animals of a particular phenotype can never be made, the intent is to provide art taught reasoning as to why the instant claims are not enabled. Given such species differences in the expression of a transgene, particularly when taken with the lack of guidance in the specification for any transgenic non-human animal whose genome comprises a non-native gene sequence coding for DAX-1 , other than the exemplified transgenic mouse, it would have required undue experimentation to predict the results achieved in any one host animal comprising and expressing DAX-1, the levels of the transgene product, the consequences of that product, and therefore, the resulting phenotype.

The Amount of Experimentation Necessary. The instant specification teaches the rescue of a phenotype in flies, but does not teach a correlation between DAX-1 and any specific neurodegenerative disease. Additionally, the specification does not teach that the non-human animal has a reduced risk of developing symptoms to a neurodegenerative disease simply by over-expression of DAX-1. The methods that are instantly claimed are not enabled because one of skill in the art would not be able to predictably produce a genetically-altered non-human animal of a specific phenotype, such that it could be used in the claimed methods. Furthermore, the broadest embodiments of the claimed invention recite no phenotype for the claimed animal; therefore, one of skill in the art would have had to utilize undue experimentation to produce a genetically altered non-human animal of the kind claimed, with an unpredictable and unknown phenotype, for use in the methods claims. Accordingly, one of skill in the art, given the breadth of animals encompassed by the claims, could not predict the resultant phenotype of introducing a DAX-1 transgene into any animal. If the phenotype is not

predictable, then use of an animal without a predictable phenotype would also be considered unpredictable.

Accordingly, in view of the state of the art with regard to producing the sheer number of animals encompassed by the claims, the undeveloped and unpredictable state of the art, with regard to the generation of any non-mammalian transgenic animal, or invertebrate, or even insect, the unpredictable state of the art with regard to producing a transgenic animal with a particular phenotype, the lack of working examples or guidance provided by the instant specification to overcome these art-recognized unpredictibilities, it would have required undue experimentation for one of skill in the art to make and use the claimed invention.

Written Description

Claims 4-8, 12 and 19-23 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

Vas-Cath Inc. v. Mahurkar 19USPQ2d 1111 (Fed. Cir. 1991), clearly states that, "[A]pplicant must convey with reasonable clarity to those skilled in the art that, as of the filing date sought, he or she was in possession of *the invention.* The invention is, for purposes of the 'written description' inquiry, *whatever is now claimed.*" *Vas-Cath Inc. v. Mahurkar,* 19USPQ2d at 1117. The specification does not, "clearly allow persons of ordinary skill in the art to recognize that [he or she] invented what is claimed." *Vas-cath Inc. v. Mahurkar*, 19USPQ2d at 1116.

The claims require a genetically altered non-human animal comprising a gene sequence coding for DAX-1, a fragment, derivative or variant thereof. Specific embodiments recite that the animal has a phenotype of a predisposition to developing symptoms of neuropathology similar to a neurodegenerative disease

(claim 6) and wherein the animal has a reduced risk of developing symptoms similar to a neurodegenerative disease due to an effect caused by the expression of the gene used to genetically alter the non-human animal (claim 7). The specification teaches utilizing full length DAX-1 cDNA to produce transgenic flies and transgenic mice. However, the genus of DAX-1 fragments, derivatives or variants thereof, which, when constructed and used as claimed, to produce a non-human animal, and specifically a transgenic animal with specifically claimed phenotypes, lacks a written description, and as such, there is no indication that Applicants had possession of the claimed invention. The claimed invention as a whole is not adequately described if the claims require essential or critical elements which are not adequately described in the specification, and are not conventional in the art **as of Applicants' effective filing date.** Possession may be shown by actual reduction to practice, clear depiction of the claimed invention in a detailed drawing, or by describing the invention with sufficient, relevant, identifying characteristics (as it relates to the claimed invention as a whole), such that one of skill in the art would recognize that the inventor had possession of the claimed invention. Pfaff v. Wells Electronics, Inc., 48 USPQ2d 1641, 1646 (1998). In the instant case, the breath of the genus of fragments, derivatives or variants of DAX-1 lacks a written description.

The skilled artisan cannot envision the detailed chemical structure of all of the fragments, derivatives and/or variants of DAX-1 that are encompassed by the claims, and therefore, conception is not achieved until reduction to practice has occurred, regardless of the complexity or simplicity of the method. Adequate written description requires more than a mere statement that it is part of the invention, and a reference to a potential method of isolating it. See *Fiers v. Revel,* 25 USPQ2d 1601, 1606 (Fed. Cir. 1993) and *Amgen Inc. v. Chugai Pharmaceutical Co. Ltd.*, 18 USPQ2d 1016 (Fed. Cir. 1991).

One cannot describe what one has not conceived. See *Fiddes v. Baird*, 30 USPQ2d 1481, 1483. In *Fiddes*, claims directed to mammalian FGFs were found to be unpatentable due to lack of written description for that broad class. The specification only provided the bovine sequence.

Applicant is reminded that *Vas-Cath* makes clear that the written description of 35 U.S.C. 112 is severable from its enablement provision [see p. 1115].

Claim Rejections - 35 USC § 112

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 6-7 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claim 6 is unclear. The phrase "displaying symptoms of neuropathology similar to a neurodegenerative disease" is unclear. The term "similar" is a relative term, and therefore, it is unclear how similar a pathology must be to a neurodegenerative disease to define the metes and bounds of the claim.

Claims 6-7 recite the term "and/or" various places throughout the claim. This phrase is unclear because it fails to set forth whether this term what this term is meant to limit or exclude, versus what it is meant to include. Appropriate correction is requested.

Claim 8 is incomplete. The claim lacks active method steps to relate to the preamble. In particular, it is unclear how using a genetically altered non-human animal relates to developing diagnostics and therapeutics to treat neurodegenerative diseases. Appropriate correction is requested.

Conclusion

No claim is allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Thaian N. Ton whose telephone number is (571)272-0736. The examiner can normally be reached on 9-5:30 M-F.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Peter Paras can be reached on 571-272-4517. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/Thaian N. Ton/
Primary Examiner, Art Unit 1632